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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/945,459	12/09/97	MAKISHIMA	F 146.1275

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EXAMINER	
ROMEO, D	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/945,459	Applicant(s) Makishima et al.
	Examiner David S. Romeo	Group Art Unit 1646

☒ Responsive to communication(s) filed on *10-21-98* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-15* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *7*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-15 are pending and are being examined.

2. The abstract of the disclosure is objected to because it is not a single paragraph. A new abstract that is a single paragraph is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

3. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-15 are indefinite because it is unclear if the protein of claim 1 has the amino acid sequence of SEQ ID NO:1 or has some portion thereof. The metes and bounds are not clearly set forth. It is suggested that claim 1 recite --A protein having the amino acid sequence--.

Claim 2 recites the limitation "homodimer protein" in line 1. There is insufficient antecedent basis for this limitation in the claim. It is suggested that the claim recite --A protein according to claim 1 wherein said protein is a homodimer--.

Claims 3-7 are indefinite because it is unclear what therapeutic effect is intended by "a therapeutically effective amount" in claim 3; an intended use is not the same as a therapeutic effect; in the absence of a recitation as to any therapeutic effect, or an effective amount of the

agent to cause a therapeutic effect, it is unclear what therapeutic effect can be inferred. It is suggested that claim 3 recite --comprising an amount of the protein according to claim 2 effective to treat said diseases--.

Claims 4, 6, 7, 12 and 14 are indefinite and/or ambiguous because osteoporosis, bone fracture, bone defect, radicular and arvecular defects are not cartilage diseases. The metes and bounds are not clearly set forth.

Claims 5, 7, 13 and 15 are indefinite and/or ambiguous because osteoarthritis, arthrosteitis, and radicular and arvecular defects are not bone diseases. The metes and bounds are not clearly set forth.

Claims 7 and 15 are indefinite because it unclear what is intended by "radicular" and "arvecular" defects. The terms do not appear to be commonly used or do not appear to have an unambiguous meaning in the art and their meaning is unclear. The metes and bounds are not clearly set forth.

Claims 9 and 10 are indefinite because it is unclear if the DNA in the phrase "DNA coding amino acid sequence" encodes the amino acid sequence of SEQ ID NO:1 or some portion thereof. It is suggested that the claims recite --a DNA encoding a polypeptide, wherein said polypeptide has the amino acid sequence of SEQ ID NO:1--.

Claims 11-15 are indefinite because they lack a process step which clearly relates back to the claim preamble and it is unclear what process is to be achieved; an intended use is not the

same as achieving a result; in the absence of a recitation as to any result, or a process step producing a result, it is unclear what result of the process can be inferred.

Claims 11-15 are indefinite because it is unclear what effect is intended by "an effective amount"; an intended use is not the same as an effect; in the absence of a recitation as to any effect, or an effective amount of the agent to cause an effect, it is unclear what therapeutic effect can be inferred. It is suggested that the claim recite --comprising an amount of the protein according to claim 2 effective to treat said diseases--.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 2, 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Hötten et al. (2, cited by Applicants). The transitional term "having" is inclusive or open-ended and does not exclude additional, unrecited elements or amino acids. Hötten et al. teach the amino acid sequence of a protein, GDF-5, having the amino acid sequence of SEQ ID NO:1 (see Figure 1 of Hötten et al.), as recited in claim 1 and as indicated below:

```
RESULT    1
ENTRY             JC2347     #type complete
TITLE             growth/differentiation factor 5 - human
ORGANISM          #formal_name Homo sapiens #common_name man
DATE              20-Feb-1995 #sequence_revision 20-Feb-1995 #text_change
                    13-Mar-1998
ACCESSIONS        JC2347
REFERENCE         JC2347
   #authors       Hoetten, G.; Neidhardt, H.; Jacobowsky, B.; Pohl, J.
   #journal       Biochem. Biophys. Res. Commun. (1994) 204:646-652
   #title         Cloning and expression of recombinant human
                    growth/differentiation factor 5.
   #accession     JC2347
      ##molecule_type DNA
      ##residues      1-501 ##label HOE
GENETICS
   #introns       211/1
KEYWORDS          glycoprotein
FEATURE
   189                 #binding_site carbohydrate (Asn) (covalent) #status
                         predicted\
   381-382             #cleavage_site Arg-Ala (unidentified proteinase) #status
                         predicted
SUMMARY           #length 501  #molecular-weight 55410  #checksum 5334

 Query Match           100.0%;  Score 900;  DB 2;  Length 501;
 Best Local Similarity 100.0%;  Pred. No. 6.99e-169;
 Matches   119;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;

Db    383 PLATRQGKRPSKNLKARCSRKALHVNFKDMGWDDWIIAPLEYEAFHCEGLCEFPLRSHLE 442
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy      1 PLATRQGKRPSKNLKARCSRKALHVNFKDMGWDDWIIAPLEYEAFHCEGLCEFPLRSHLE 60

Db    443 PTNHAVIQTLMNSMDPESTPPTCCVPTRLSPISILFIDSANNVVYKQYEDMVVESCGCR 501
          |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy     61 PTNHAVIQTLMNSMDPESTPPTCCVPTRLSPISILFIDSANNVVYKQYEDMVVESCGCR 119
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Hötten et al. teach that native GDF-5 is a dimer of the disulfide linked mature part of the protein as is seen in other members of the TGF-β superfamily of proteins and that comparison of other polybasic processing sites among TGF-β superfamily members strongly suggests a mature protein of 120 amino acids, as recited in claim 2 (page 650, first full paragraph and first paragraph of discussion; Figure 5). Hötten et al. also teach a six histidine tagged fragment of GDF-5 comprising the mature portion of GDF-5 (page 647, full paragraph 2). The six histidine tagged

fragment is also a protein having the amino acid sequence of SEQ ID NO:1. Hötten et al. teach a process for preparing the six histidine tagged fragment of GDF-5 comprising culturing *E. coli* transformed with a plasmid containing a DNA sequence which is capable of expressing said fragment, as recited in claim 8 (page 647, full paragraph 2; paragraph bridging pages 649-650). The six histidine tagged fragment of GDF-5 would have to have a methionine at the N-terminus, as recited in claim 9, because the synthesis of all proteins begins with a methionine at the N-terminus.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 2 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hötten et al. (2, cited by Applicants) as applied to claims 1 and 2 above and further in view of Cerletti et al. (N). Hötten et al. teach a dimer of GDF-5, which is a TGF-β-like protein, and a plasmid containing DNA encoding a six histidine tagged fragment of GDF-5 with a methionine at the N-terminus, as discussed above. Hötten et al. do not teach a process for preparing a GDF-5 dimer,

as recited in claim 10. Cerletti et al. teach a process for the production of biologically active, dimeric TGF-β-like proteins. The process comprises culturing an *E. coli* host that has been transformed with a plasmid containing DNA encoding the amino acid sequence of a TGF-β-like protein (page 7, lines 40-41), solubilizing inclusion bodies obtained by culturing said *E. coli*, purifying the monomer protein from the solubilized solution, refolding the monomer protein into a dimer protein, and purifying same (page 7, line 56 through page 8, line 15). Cerletti et al. do not teach a process for preparing a dimer of GDF-5. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to construct a plasmid containing DNA coding amino acid sequence in SEQ ID NO:1 of the sequence listing with a methionine at the N-terminus, as taught by Hötten et al., and to modify that teaching by forming a dimer, as taught by Cerletti et al., with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings in order to form a homodimer of GDF-5, the native form of the molecule. The invention is prima facie obvious over the prior art.

8. Claims 1-7 and 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hötten et al. (2, cited by Applicants) as applied to claims 1 and 2 above, and further in view of Neidhardt et al. (1, cited by Applicants).

Hötten et al. teach a protein, GDF-5, and teach that the native form of GDF-5 is a dimer, as discussed above. Hötten et al. do not teach a pharmaceutical composition comprising a

homodimer of GDF-5 and a pharmaceutically acceptable carrier. Hötten et al. do not teach administering such a pharmaceutical composition to a human.

Neidhardt et al. (1, cited by Applicants) teaches a protein, MP-52, having the amino acid sequence of SEQ ID NO:1 as indicated below:

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RESULT    5
ID   R40800 standard; Protein; 401 AA.
AC   R40800;
DT   11-FEB-1994  (first entry)
DE   TGF-β-like clone MP-52 protein.
KW   Human; transforming growth factor; β; TGF-β; pharmaceutical;
KW   bone; cartilage; tooth; wound repair; immunosuppressor;
KW   organ transplant; cosmetic surgery; antibody; diagnosis.
OS   Homo sapiens.
PN   WO9316099-A.
PD   19-AUG-1993.
PF   12-FEB-1993; E00350.
PR   12-FEB-1992; EP-102324.
PA   (BIOP-) BIOPHARM GES BIOTECHNOLOGISCHEN ENTWICKL.
PI   Hoetten G,  Neidhardt H;
DR   WPI; 93-272824/34.
DR   N-PSDB; Q47709.
PT   New transforming growth factor-beta family proteins and DNA -
PT   used in tissue and wound repair, in treatment of bone, cartilage
PT   and tooth defects, and antibodies for diagnosis
PS   Claim 11; Page 19; 29pp; English.
CC   The sequences given in R40800 and R45447 represent frements of embryo
CC   and liver derived human transforming growth factor-beta (TGF-beta)
CC   respectively.  The full length protein may be used in a pharmaceutical
CC   composition for the treatment of various bone, cartilage or tooth
CC   defects and in tissue and wound repair processes.  These proteins may
CC   also be used as immunosuppressors in organ transplants and in cosmetic
CC   surgery.  Antibodies raised against these proteins may be used for
CC   diagnostic purposes.
SQ   Sequence   401 AA;

  Query Match          100.0%;  Score 900;  DB 8;  Length 401;
  Best Local Similarity 100.0%;  Pred. No. 1.66e-81;
  Matches   119;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;

Db    283 platrqgkrpsknlkarcsrkalhvnfkdmgwddwiiapleyeafhceglcefplrshle 342
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy      1 PLATRQGKRPSKNLKARCSRKALHVNFKDMGWDDWIIAPLEYEAFHCEGLCEFPLRSHLE 60

Db    343 ptnhaviqtlmnsmdpestpptccvptrlspisilfidsannvvykqyedmvvescgcr 401
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy     61 PTNHAVIQTLMNSMDPESTPPTCCVPTRLSPISILFIDSANNVVYKQYEDMVVESCGCR 119
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Neidhardt et al. disclose the mature portion of MP-52 and most of the propeptide sequence (bottom half of page 3). Based on the amino acid sequence identity between Neidhardt et al's. MP-52 and Hötten et al's. GDF-5 one of ordinary skill in the art would reasonably expect that Neidhardt et al's. MP-52 is Hötten et al's. GDF-5. Neidhardt et al. teach a pharmaceutical composition comprising MP52 and a pharmaceutically acceptable carrier for use in the healing of bone, cartilage, or tooth defects and discloses the administration of such a composition to humans (page 9, full paragraph 1). Neidhardt et al. do not teach a pharmaceutical composition comprising a homodimer of GDF-5 and a pharmaceutically acceptable carrier. Neidhardt et al. do not teach administering such a pharmaceutical composition to a human. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a dimer of GDF-5, as taught by Hötten et al., and to modify this teaching by making a pharmaceutical composition comprising a dimer of GDF-5 and a pharmaceutically acceptable carrier, and to administer such a composition to a human, as taught by Neidhardt et al., with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings because the native form of GDF-5 is a dimer and in order to achieve the therapeutic effects taught by Neidhardt et al. The intended uses of the claimed pharmaceutical compositions and methods do not patentably distinguish such compositions and methods over the compositions and methods of the prior art. Furthermore, the prior art teaches the sole, recited process step of

administering the protein and one would reasonably expect the process step to achieve the intended use.

Conclusion

9. No claims are allowed.

10. The results of Applicants process of making a protein consisting of the amino acids sequence of SEQ ID NO:1 (page 2, last paragraph through page 3, first paragraph) are unexpected and claims limited to such a process may be allowable over the prior art.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Sherman et al. (V) teach that the synthesis of all proteins from all living cells begins with methionine (page 27, column 1, first sentence of introduction). Celeste et al. (A) teach a protein, MP52, which contains amino acids #1 to #120 of Celeste et al's. SEQ ID NO:4. Amino acids #2 to #120 of Celeste et al's. SEQ ID NO:4 are identical to applicants' SEQ ID NO:1. Celeste et al. also teach that the first cysteine of the seven cysteine domain of MP52 is encoded by the codon beginning at nucleotide #899 of SEQ ID NO:3 (column 7, full paragraph 3). The codon beginning at nucleotide #899 of SEQ ID NO:3 encodes amino acid #19 of SEQ ID NO:4. Celeste et al. also teach human MP52 proteins containing the amino acid sequence from amino

acid #17 or #19 to #119 or #120 of SEQ ID NO:4 are expected to retain activity (column 7, full paragraph 3). Özkaynak et al. (U) teach the N-terminal residues upstream of the 7-cysteine domains of the mature proteins in the TGF-β superfamily (Figure 4) and teach that the mature N-termini of different members of the TGF-β superfamily are quite diverse, that the N-termini have diverged because they are not crucial for receptor binding or protein folding, and that the N termini are not essential for biological activity (page 25226, column 2, full paragraphs 2-3).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David S. Romeo whose telephone number is (703) 305-4050. The examiner can normally be reached on Monday through Thursday from 6:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731.

Official papers filed by fax should be directed to (703) 308-4242.

Faxed draft or informal communications should be directed to the examiner at (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

David Romeo

DSR
December 9, 1998